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(54) Title: TOPICAL ANTIFUNGAL COMPOSITION

(57) Abstract

The invention relates to a topical, foamable composition including at least one antifungal agent, said composition characterised in that said at least one antifungal agent is able to penetrate the upper layers of skin and is retained in or on an area to be treated for a prolonged period of time, and in that it has a residual non-volatile component content of less than 25 %. The invention furthermore relates to a method of treating fungal diseases including jock itch, tinea, dandruff and sebborheic dermatitis by applying to the affected area of a patient requiring such treatment the antifungal composition as claimed in any one of claims 1–29.

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T pical Antifungal Compositi n

Background of the Invention

The present invention relates to a foamable antifungal composition for the treatment of various skin conditions.

Antifungal agents are well known, and include macrolide antibiotics such as griseofulvin, and imidazoles such as clotrimazole and ketoconazole.

Ketoconazole was originally described by Heeres *et al* in US patent 4,335,125, in which its principal utility was an antifungal compound useful in the treatment of a variety of conditions including sebborheic dermatitis, dandruff, "jock itch" and tinea.

Antifungal compositions are traditionally applied as lotions or creams. There are however disadvantages to these forms. In particular, the formulations are frequently very viscous requiring substantial rubbing to achieve penetration into the effected area, an act in itself which causes discomfort and sometimes irritation. If the viscous formulations are not vigorously applied, the active antifungal agent does not necessarily reach the site requiring treatment being the epidermis of the skin. Non-viscous creams and lotions are wont to flow off the effected site before penetration is achieved. One final disadvantage is that cream and lotion bases in themselves can add to site irritation depending on their content.

Ketoconazole was disclosed in US patent 4,569,935 to be useful in the topical treatment of psoriasis and seborrheic dermatitis. Pursuant to this utility, ketoconazole has been marketed in a 2% shampoo formulation for the treatment of scaling due to dandruff, sold under the brand name "Nizoral®". This shampoo is applied by the user and then removed shortly, for example 3-5 minutes, after its application by rinsing with water. The active agent is thus only in contact with the area to be treated for a very limited time.

Another patent describing ketoconazole based shampoos is US5,456,851 in the name of JOHNSON & JOHNSON CONSUMER PRODUCTS, INC which aims to provide good cosmetic properties to the shampoo including lather, and to retard degradation of the ketoconazole. This composition is a foaming formulation.

The disadvantage of such shampoo formulations is that during normal usage, the formulation does not remain on the scalp for a period of time sufficient to allow the antifungal agent to achieve its maximal therapeutic effect since they are designed to be applied, for example in the shower or bath, and shortly after rinsed off with water. Typically, the application instructions for such shampoos suggest that the formulation be removed after 3-5 minutes.

In order to achieve maximal therapeutic effect, one alternative such as is described in AU 80257/87, is to provide a high quantity of residual solids which remain after application to treat the offending skin condition. There is disclosed in AU 80257/87 a foam composition for the delivery of minoxidil. The formulations disclosed in this document all contain a high percentage of non-volatile residues, including propylene glycol. While it is not disclosed why these formulations contain such a large amount of propylene glycol, it is postulated that the propylene glycol is probably required either to enhance the penetration and/or to improve the solubility of the minoxidil. The disadvantage of a composition with a high residual content is that the non-volatile residues are retained at the site of application and therefore feel unpleasant and unattractive to the user.

Alternatives to ketoconazole and minoxidil are decribed in AU-A-35717/93 in the name of SMITH KLINE BEECHAM PLC which discloses compositions including a novel androstene steroid for use in the treatment of acne and sebborrhea, and AU-A-48851/96 in the name of MEDEVA PLC which describes the use of betamethasone in a quick breaking foam including a buffering agent for use in the treatment of skin diseases and particularly scalp psoriasis.

It is an aim of this invention to provide an antifungal composition which is effective in its treatment of fungal skin conditions but which is also pleasant to use.

Summary of the Invention

To this end, in a first aspect of the invention, there is provided a topical, foamable composition including at least one antifungal agent, said composition characterised in that said at least one antifungal agent is able to penetrate the

upper layers of the skin and is retained in or on an area to be treated for a prolonged period of time, and in that it has a residual non-volatile component content of less that 25%.

It has been surprisingly found that the antifungal composition of the present invention has a commercially acceptable cosmetic appeal and during normal usage allows greater penetration and retention of the antifungal agent in the upper layers of the skin, particularly in the epidermis, thus providing a reservoir of active agent available to achieve a sustained antifungal effect when compared against known formulations. This latter feature leads to enhanced pharmaceutical appeal as well as cosmetic appeal. Moreover, the residual solids content of the formulation is so low as to not provide discomfort and irritation to the user

The term "prolonged period of time" is meant to encompass periods of time sufficiently long so as to enable the active agent present to be substantially fully absorbed by the organism being treated, or substantially fully metabolised by the patient being treated.

In a preferred embodiment, the one or more antifungal agents is selected from the group consisting of diols, allylamines (including naftifine and terbinafine), polyene macrolide antibiotics (including amphotericin and nystatin), triazole derivatives (such as fluconazole), fatty acids (such as caprylic and propionic acid), amorolfine, ciclopirox, olamine, benzoic acid, flucytosine, haloprogin, tolnaftate, undecenoic acid and its salts, griseofulvin and imidazole compounds. More preferably, the antifungal is an imidazole compound. Most preferably, the antifungal agent is ketoconazole or chlorphenesin (3-(4-Chlorphenoxy)propane-1,2-diol).

Preferably the compositions according to the invention have a residual non-volatile component content of less that 10%, and more preferably of less than 6%.

In a preferred embodiment the topical, foamable composition is provided as a mousse.

In a further preferred embodiment the mousse is a temperature sensitive mousse, which breaks down rapidly when exposed to the skin temperature.

In a still further embodiment, the composition is an ethanolic mousse including a lower alcohol content of greater than 10%, more preferably greater than 50% and a hydrocarbon gas content propellent of less than 60%, more preferably less than 10%.

In an alternative embodiment the composition is an aqueous mousse including no lower alcohol content and a hydrocarbon gas content propellent of less than 60%, more preferably less than 10%.

(Unless specified otherwise in the specification, all % are based on the total weight of the composition.)

In the temperature sensitive mousse, the long chain alcohol may be chosen from, for example, cetyl, stearyl, lauryl, myristyl and palmityl alcohols and mixtures of two or more thereof.

The lower alcohol may preferably be chosen from methyl, ethyl, isopropyl and butyl alcohols, and mixtures of two or more thereof. Ethanol has been found to be particularly preferred.

Surfactants utilised in the temperature sensitive mousse may preferably be chosen from ethoxylated sorbitan stearate, palmitate, oleate, nonyl phenol ethoxylates and fatty alcohol ethoxylates, and mixtures of two or more thereof. Thus, for example, Polysorbate 60 (a mixture of partial stearic esters of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides) has been found to be particularly preferred. The surfactant enhances the long chain alcohol solubility in the system and enhances mousse formation.

In a further aspect of the invention, there is provided a foamable composition including

up to 5% of long chain alcohols	= cetyl / stearyl alcohol	@ 1.16/0.53%
up to 5% of quaternary compound	= Dehyquart SP	Polysorbate 60
up to 10% of propylene glycol	=	2.11
up to 5% of antifungal agent	= Keto	2%
up to 90% of lower alcohol solvent	= Ethyl	
up to 5% of surfactant	= eg. Polysorbate 60	Pas 0.42%
5-95% of water, and		

up to 20% of a hydrocarbon gas propellant

Preferably, the long chain alcohol is cetyl or stearyl alcohol or mixtures thereof.

Preferably, the quaternary compound is quaternium oxy ethyl alkyl ammonium phosphate commercially available under the trade name, Dehyquart SP.

Preferably, the lower alcohol solvent is ethanol or propanol or mixtures thereof.

Suitable gas propellants include non-toxic gas propellants suited to foamable cosmetic and pharmaceutical compositions and known to those skilled in the art.

Thus, one may select the propellant from propane, butane, dichloro difluoro methane, dichloro tetrafluoro ethane, octafluoro cyclobutane, and mixtures of two or more thereof. It is necessary to select a propellant most compatible with the entire system. The maximum level of propellant will be determined as the amount miscible with the utilized water/lower alcohol ratio. In addition to acting as a propellant, the propellant will also act as a solvent for the long chain alcohol and active substances in the aqueous/alcoholic system.

In a second aspect of the invention there is provided a composition for the treatment of fungal skin conditions including dandruff, seborrheic dermatitis, tinea, jock itch and the like, said composition characterised in that it is a foamable mousse applicable to the skin of the user in the substantial absence of water and without substantially immediate removal by washing.

In a preferred embodiment of this aspect of the invention, said composition has a non-volatile component content of less than 25%, preferably less than 10% and more preferably less than 6%.

In a more preferred embodiment of this aspect of the invention, the mousse is a temperature sensitive mousse, which breaks down rapidly when exposed to the skin temperature.

In a still further preferred embodiment, the composition is a mousse including a lower alcohol content of greater than 10%, more preferably greater than 50% and a hydrocarbon gas content propellent of less than 60%, more

preferably less than 10%.

In a further aspect of the invention there is provided a topical, foamable composition including an antifungal agent characterised in that upon application to the skin of a user a penetration of at least 10μg/cm^2 is achieved in the epidermis within one hour of application and sustained over a period of at least 23 hours.

When the preferred active agent is ketoconazole, the invention provides a topical, foamable composition characterised in that upon application to the skin of a user a penetration of at least 30μg/cm^2 is achieved in the epidermis within one hour of application and sustained over a period of at least 23 hours.

When the preferred active agent is chlorphenesin, the invention provides a topical, foamable composition characterised in that upon application to the skin of a user a penetration of at least 10μg/cm^2 is achieved in the epidermis within one hour of application and sustained over a period of at least 23 hours.

In a still further aspect of the invention, there is provided a method of treating fungal infections, particularly tinea, jock itch, dandruff and sebborheic dermatitis by applying to the affected area of a patient requiring such treatment the antifungal composition of the present invention.

In a preferred embodiment of this aspect of the invention, the composition is allowed to remain on the affected area for an extended period of time.

In this context "extended period of time" means a length of time greater than the length of time that prior art topical compositions such as shampoos are prescribed to remain in contact with the affected area. Usually, shampoos are designed to be washed off within 5 minutes.

More preferably, when the composition is used to treat dandruff or sebborheic dermatitis, it is applied at one wash or between washes and is allowed to remain on the site of application such as the scalp or hair until the site of application is subsequently washed again.

The invention also encompasses the use of an antifungal agent in the preparation of a topical foamable composition for the treatment of fungal diseases including dandruff, tinea, jock itch and sebborheic dermatitis, the topical foamable composition being characterised in that it is able to penetrate

the epidermis of the skin and is retained in or on an area to be treated for a prolonged period of time, and in that it has a non-volatile component content of less that 25%.

Detailed Description of the Invention

Two formulations of the present invention were prepared.

1) 0.5% ketoconazole mousse composition

Cetyl alcohol	1.10
Stearyl alcohol	0.50
Quaternium 52 (50%)	1.00
Propylene Glycol	2.00
Ketoconazole USP	0.50
Ethanol 95PGF3	60.55
Deionised Water	30.05
P75 Hydrocarbon Propellant	4.30

2) 1% ketoconazole mousse composition

Cetyl alcohol	1.10
Stearyl alcohol	0.50
Quaternium 52 (50%)	1.00
Propylene Glycol	2.00
Ketoconazole USP	1.00
Ethanol 95PGF3	60.20
Deionised Water	29.90
P75 Hydrocarbon Propellant	4.30

The compositions were prepared by dissolving the active in the ethanol. the cetyl and stearyl alcohol are then added to the heated solution and mixed until dissolved. The quaternium 52, propylene glycol and water are then added and stirred until homogenous, while maintaining the elevated temperature. The solution is then dispensed into aerosol cans where the aerosol valve is then fitted and the can charged with propellant.

EXAMPLE 1

A study was undertaken to compare the epidermal penetration of the two mousse compositions above, against the commercially available Nizoral®

shampoo containing 2% ketoconazole. In particular the respective formulations were applied and removed as for a conventional shampoo so as to compare the penetration of the respective formulations into the epidermis.

Equipment and Materials

in vitro Franz diffusion cells (surface area 1.33 cm^2, receptor volume 3.5ml) incorporating human epidermis

HPLC equipment: Shimadzu automated HPLC system with uv detector, bovine serum albumin dissolved in phosphate buffered saline (pH 7.4) as receptor phase to mimic physiological conditions.

Experimental Protocol

finite dosing (50mg for shampoo and 100mg for mousses)

receptor phase: 4% BSA in phosphate buffered saline at pH 7.4 sampling time: 6,10,24 hours (amount in receptor phase (µg/cell) and epidermis(µg/cell)) non-occlusion study

each time period and formulation conducted in triplicate.

Application Procedure

Shampoo: 50 mg shampoo (equivalent to 1 mg ketoconazole)
dose applied to pre-wetted skin with stirring and rinsed off with deionised water after 4 minutes.

Mousse: 100 mg mousse (equivalent to 1 mg ketoconazole for 1% mousse and 500 µg ketoconazole for 0.5% mousse
dose applied (not rinsed off).

Epidermal retention protocol

Epidermis removed from cell following time interval, rinsed with distilled water and dried to remove ketoconazole remaining on surface. Ketoconazole extracted from epidermal sample by soaking in methanol for 1 hour. This procedure is repeated with a second volume of methanol for 30 mins. The methanol samples are combined for HPLC analysis (this procedure has been validated with a 99% recovery rate).

HPLC assay

Column: Nova Pak C_{18} steel column, 3.9 x 150 mm

Mobile phase: 70% MeOH in 0.02 M phosphate buffer, pH 6.8

Wavelength: 254 nm

Flow rate: 1.3 ml/min

Injection volume: 10 µl

Retention time: about 7 min

Results

Table 1 shows the cumulated ketoconazole in both the receptor phase and the epidermis at defined time points following application of the mousse according to the invention and the shampoo of the prior art.

TABLE 1

	Ketoconazole µg/cell					
	6 hours		*10 hours*		*24 hours*	
Sample	receptor	epidermis	receptor	epidermis	receptor	epidermis
0.5% mousse	4.96	33.15	9.04	69.46	14.69	42.10
0.5% mousse	2.83	35.71	18.06	48.04	24.77	39.19
0.5% mousse	14.37	34.3	21.3	55.29	9.82	48.27
Mean±SD	7.4±6.1	34.4±1.3	16.1±6.4	57.6±10.9	16.4±7.6	43.2±4.6
1% mousse	12.86	46.4	31.50	67.51	21.90	51.43
1% mousse	10.03	61.8	11.05	55.65	35.85	46.64
1% mousse	18.61	38.6	19.38	56.83	10.72	43.28
Mean±SD	13.8±4.4	48.9±11.8	20.6±10.3	60±6.5	22.8±12.6	47.1±4.1
2% shampoo	N	N	N	0.89	N	N
2% shampoo	N	N	N	0.28	N	0.38
2% shampoo	N	N	N	N	N	0.34
Mean±SD	-	-	-	0.39±0.46	-	0.24±0.21

N: not detectable (assuming to be zero for calculating mean and SD)

-: not available

Table 2 shows the cumulated ketoconazole in both receptor (expressed as µg/ml receptor fluid) and epidermis (expressed as µg/cm² surface area) at defined time points following application of the mousse according to the present invention and the shampoo of the prior art.

TABLE 2

	Ketoconazole µg					
	6 hours		*10 hours*		*24 hours*	
Sample	receptor	epidermis	receptor	epidermis	receptor	epidermis
0.5% mousse	1.42	26.95	2.58	56.47	4.20	34.23
0.5% mousse	0.81	29.03	5.16	39.06	7.08	31.86
0.5% mousse	4.11	27.89	6.09	44.95	2.81	39.24
Mean±SD	2.11±1.76	27.96±1.04	4.61±1.82	46.83±8.86	4.70±2.18	35.11±3.77
1% mousse	3.67	37.72	9.00	54.89	6.26	41.81
1% mousse	2.87	50.24	3.16	45.24	10.24	37.92
1% mousse	5.32	31.38	5.54	46.20	3.06	35.19
Mean±SD	3.95±1.25	39.78±9.60	5.90±2.94	48.78±5.31	6.52±3.60	38.31±3.33
2% shampoo	N	N	N	0.72	N	N
2% shampoo	N	N	N	0.23	N	0.31
2% shampoo	N	N	N	N	N	0.28
Mean±SD	-	-	-	0.32±0.37	-	0.20±0.17

N: not detectable (assuming to be zero for calculating mean and SD)

-: not available

Figure 1 shows the time course of the ketoconazole penetrating across human epidermis to receptor fluid. The closed points of the graph represent 0.5% mousse, the open points represent 1.0% mousse. Data are the mean ± SD of triplicate (from Table 2).

Figure 2 represents the time course of ketoconazole retained in the epidermis. The closed points of the graph represent 0.5% mousse, the open points represent 1.0% mousse. Data are the mean ± SD of triplicate (from Table 2).

Figure 3 compares the levels of retention of ketoconazole on the skin, the levels of retention of the ketoconazole in the skin and the amount of ketoconazole passed through the skin in the tests using a mousse according to the invention with the same measures using Nizoral®. Note that ketoconazole levels found after application of the Nizoral® shampoo were low and thus are not visible in this figure

It can readily be observed from the results of example 1 that:

1. the ketoconazole in the mousse compositions of the present invention penetrated the skin in appreciable quantity;
2. the ketoconazole in the mousse composition of the present invention was preferentially retained in the epidermis compared to penetration into the receptor solution;
3. application of the prior art shampoo, Nizoral®, resulted in insignificant amounts of ketoconazole in the epidermis and penetrating to the receptor phase at any of the time points following application using a standardised shampooing procedure;
4. comparison of the 1% and 0.5% mousse formulations of the present invention shows that there is little difference in epidermal and receptor phase concentrations.

EXAMPLE 2

A second study was undertaken to compare the skin penetration and retention of ketoconazole from the 1% ketoconazole mousse composition of the current invention with Nizoral® Shampoo (1%w/w). The 1% mousse composition had a total residue content of 5.1% solids including active.

Equipment and Materials

In vitro Franz diffusion cells (surface area 1.33 cm^2, receptor volume 3.5 mL) incorporating full thickness human skin,

HPLC equipment: Shimadzu automated HPLC system with uv detector.

Experimental protocol

Finite dosing (50 mg of each formulation placed onto skin surface),

Receptor phase: 4% bovine serum albumin (BSA) in phosphate buffered saline (PBS) pH 7.4,

Sampling times for skin retention: 15 minutes, 1, 12, 24 hours,

Sampling times for skin penetration to receptor phase: 12, 24 hours,

Amount of ketoconazole in full thickness skin and receptor phase measured by HPLC assay following suitable extraction procedure,

Non-occlusion study,

Triplicate measurements.

Application procedure

Both mousse and shampoo were applied and left in contact with the skin for the duration of the penetration study. Following this the formulation was washed off the skin with distilled water prior to sample extraction procedure and HPLC assay for ketoconazole content.

HPLC assay

Column:	Nova Pac C_{18} steel column, 3.9 x 150 mm (Waters)
Mobile phase:	70% MeOH in 0.02M PBS, pH 6.8
Wavelength:	254 nm
Flow rate:	1.0 mL/min
Injection volume:	10 µL
Retention time:	approximately 8 mins

Full thickness skin retention protocol

Full thickness skin was removed from cell following time interval, rinsed with distilled water and dried to remove ketoconazole remaining on surface. Ketoconazole was extracted from full thickness skin sample by soaking in methanol for 1 hour. This procedure was repeated with a second volume of methanol for 30 mins. The methanol samples were combined from HPLC

analysis. [This procedure has been validated with a 99% recovery rate].

Results

Figure 4 shows the HPLC standard curve for ketoconazole.

Table 3 shows the amount of ketoconazole retained in the skin (μg/cm²) at 15, 60 minutes, 12 and 24 hours following application of the mousse according to the invention, or the shampoo of the prior art.

Table 3, Ketoconazole retained in skin (μg/cm²) at 15, 60 mins, 12, 24 hours following application of mousse or shampoo.

Sample	Ketoconazole in skin (μg/cm²) mean ± SEM			
	15 mins	60 mins	12 hrs	24 hrs
Shampoo	11.2 ± 0.91	24.2 ± 1.58	39.7 ± 12.3	70.1 ± 18.8
Mousse	19.6 ± 2.5	44.1 ± 8.27	128.37 ± 19.1	228.57 ± 14.8

Table 4 shows the amount of ketoconazole penetrated to the receptor phase (μg/mL) at 12, 24 hours following application of the mousse according to the invention, or the shampoo of the prior art.

Table 4, Ketoconazole penetrated to receptor phase (μg/mL) at 12, 24 hours following application of mousse or shampoo.

Sample	Ketoconazole in receptor (μg/mL) mean ± SEM			
	15 mins	60 mins	12 hrs	24 hrs
Shampoo	-	-	n	0.04 ± 0.04
Mousse	-	-	0.07 ± 0.05	0.30 ± 0.04

n: not detectable

-: not assayed

Figure 5 shows the amount of ketoconazole retained in the skin versus the time after application of the formulation according to the invention. Data are the mean ±SEM (n=3) from Table 4.

The mousse formulation according to the invention demonstrated

significantly greater skin retention of ketoconazole than the shampoo formulation of the prior art over the 24 hour period.

It can readily be observed from the results of example 2 that:

1. penetration of ketoconazole to the receptor phase over the 24 hours following application was minimal for both shampoo and mousse.
2. skin retention of ketoconazole was significantly greater following application of the mousse formulation compared to the shampoo ($p<0.05$).

EXAMPLE 3

A third study was undertaken to compare the skin penetration and retention of two formulations according to the invention in which the active anti fungal agent was chlorphenesin (0.5% w/w). One formulation was ethanolic and had a total residue content of 2.5% solids including active, the other formulation was aqueous and had a total residue content of 4.6% solids including active.

Aqueous formulation	%w/w
Chlorphenesin	0.50
Cetyl alcohol	0.70
Stearyl alcohol	0.30
Icocetyl alcohol	2.50
Ceteth 20	0.50
Preservative	0.10
Purified Water	90.40
P75 Hydrocarbon Propellant	5.00

Ethanolic formulation	
Chlorphenesin	0.50
Cetyl alcohol	1.10
Stearyl alcohol	0.50
Polysorbate	0.40
Ethanol 95%	60.79
Purified Water	32.41
P75 Hydrocarbon Propellant	4.30

Equipment and Materials

In vitro Franz diffusion cells (surface area 1.33 cm^2, receptor volume 3.5 mL) incorporating full thickness human skin,

HPLC equipment: Shimadzu automated HPLC system with uv detector.

Experimental protocol

Finite dosing (50 mg of each formulation placed onto skin surface),

Receptor phase: 4% bovine serum albumin (BSA) in phosphate buffered saline (PBS) pH 7.4,

Sampling times for skin retention: 15 minutes, 1, 12, 24 hours,

Sampling times for skin penetration to receptor phase: 12, 24 hours,

Amount of chlorphenesin in full thickness skin and receptor phase measured by HPLC assay following extraction into acetonitrile (ACN) and methanol (MeOH) (9:1),

Non-occlusion study,

Triplicate measurements.

Application

Mousses according to the invention were applied and left in contact with the skin for the duration of the penetration study. Following this the formulation was washed off with distilled water prior to the extraction and HPLC fo chlorphenesin content.

HPLC assay

Column:	Nova Pac C_{18} steel column, 3.9 x 150 mm (Waters)
Mobile phase:	30% ACN
Wavelength:	280 nm
Flow rate:	1.0 mL/min
Injection volume:	20 µL
Retention time:	approximately 3.6 mins

Skin Retention Protocol

Skin was removed form the cell following time interval and rinsed with distilled water to remove chlorphenesin on the surface. Chlorphenesin was extracted from homogenised skin by soaking in 1mL ACN-MeOH mix for 1 hour. This procedure was repeated for a further four 30 minute periods. The five samples were combined for HPLC analysis. [The procedure was validated with a 99%

recovery rate].

Results

Figure 6 shows the HPLC standard curve for chlorphenesin. Data are the mean ± standard deviation (n=3).

Table 5 shows the amount of chlorphenesin retained in the skin (µg/cm²) at 15, 60 minutes, 12 and 24 hours following application of the mousse according to the invention.

Table 5

Sample	Chlorphenesin in skin (µg/cm²) mean ± SD			
	15 mins	60 mins	12 hrs	24 hrs
aqueous	12.8±4.8	13.2±1.1	47.6±13.2	35.8±2.2
non-aqueous	16.7±5.5	22±9.7	93.8±17.3	57.4±20.4

Table 6 shows the amount of chlorphenesin penetrated to the receptor phase (µg/mL) at 12, 24 hours following application of the mousse according to the invention.

Table 6

Sample	Chlorphenesin in receptor (µg/mL) mean ± SD			
	15 mins	60 mins	12 hrs	24 hrs
aqueous	-	-	2.9±0.4	5.6±1.1
non-aqueous	-	-	5±0.7	5.1±1.5

:- not assayed

Figure 7 shows the amount of chlorphenesin retained in the skin versus the time after application of the formulation according to the invention. Data are the mean ± standard deviation (n=3) from Table 5. The open points are the aqueous formulation. The closed points represent the ethanolic formulation.

It is readily observed from the results of example 3 that active agents other than ketoconazole formulated as both ethanolic and aqueous compositions achieve the desired penetration and retention levels for effective treatment of fungal skin conditions.

It will be appreciated that the scope of this invention goes beyond the specific formulations exemplified to encompass topical foamable antifungal compositions having like components to those specifically mentioned but having characteristic penetration and retention levels in the skin of the user, and low levels of residual solid content as defined.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A topical, foamable composition including at least one antifungal agent, said composition characterised in that said at least one antifungal agent is able to penetrate the upper layers of skin and is retained in or on an area to be treated for a prolonged period of time, and in that it has a residual non-volatile component content of less than 25%.

2. The composition as claimed in claim 1 which has a residual non-volatile component content of less than 10%.

3. The composition as claimed in claim 1 or 2 which has a residual non-volatile component content of less than 6%.

4. The composition as claimed in any one of claims 1-3 which is a mousse.

5. The composition as claimed in claim 4 wherein the mousse is a temperature sensitive mousse which breaks down rapidly when exposed to the skin temperature.

6. The composition as claimed in any one of claims 1-5 which is ethanolic.

7. The composition as claimed in any one of claims 1-5 which is aqueous.

8. The composition as claimed in any one of claims 1-6 including a lower alcohol content of greater than 10% and a hydrocarbon gas content propellent of less than 60%.

9. The composition as claimed in any one of claims 1-5 and 7 including a hydrocarbon gas content propellent of less than 60%.

10. The composition as claimed in any one of claims 1-9 including
up to 5% of long chain alcohols
up to 5% of quaternary compound
up to 10% of propylene glycol
up to 5% of antifungal agent
up to 90% of lower alcohol solvent
up to 5% of surfactant
5-95% of water, and
up to 20% of a hydrocarbon gas propellant

11. The composition as claimed in any one of claims 1-10 in which the at least one antifungal agent is selected from the group consisting of diols, allylamines (including naftifine and terbinafine), polyene macrolide antibiotics (including amphotericin and nystatin), triazole derivatives (such as fluconazole), fatty acids (such as caprylic and propionic acid), amorolfine, ciclopirox, olamine, benzoic acid, flucytosine, haloprogin, tolnaftate, undecenoic acid and its salts, griseofulvin and imidazole compounds.

12. The composition as claimed in any one of claims 1-11 in which the antifungal is an imidazole compound.

13. The composition as claimed in any one of claims 1-11 in which the antifungal agent is ketoconazole or chlorphenesin.

14. A composition for the treatment of fungal skin conditions including jock itch, tinea, dandruff and seborrheic dermatitis, said composition characterised in that it is a foamable mousse applicable to the skin of the user in the substantial absence of water and without substantially immediate removal by washing.

15. The composition as claimed in claim 14 having a non-volatile component content of less than 25%.

16. The composition as claimed in claim 14 having a non-volatile component content of less than 10%.

17. The composition as claimed in claim 14 having a non-volatile component content of less than 6%.

18. The composition as claimed in any one of claims 14-17 wherein the mousse is a temperature sensitive mousse which breaks down rapidly when exposed to the skin temperature.

19. The composition as claimed in any one of claims 14-18 which is ethanolic.

20. The composition as claimed in any one of claims 14-18 which is aqueous.

21. The composition as claimed in any one of claims 14-19 including a lower alcohol content of greater than 10% and a hydrocarbon gas content propellent of less than 60%.

22. The composition as claimed in any one of claims 14-18 and 20 including a hydrocarbon gas content propellent of less than 60%.

23. The composition as claimed in any one of claims 14-22 including
up to 5% of long chain alcohols
up to 5% of quaternary compound
up to 10% of propylene glycol
up to 5% of antifungal agent
up to 90% of lower alcohol solvent
up to 5% of surfactant
5-95% of water, and
up to 20% of a hydrocarbon gas propellant

24. The composition as claimed in any one of claims 14-23 in which the at least one antifungal agent is selected from the group consisting of diols, allylamines (including naftifine and terbinafine), polyene macrolide antibiotics (including amphotericin and nystatin), triazole derivatives (such as fluconazole), fatty acids (such as caprylic and propionic acid), amorolfine, ciclopirox, olamine, benzoic acid, flucytosine, haloprogin, tolnaftate, undecenoic acid and its salts, griseofulvin and imidazole compounds.

25. The composition as claimed in any one of claims 14-23 in which the antifungal is an imidazole compound.

26. The composition as claimed in any one of claims 14-23 in which the antifungal agent is ketoconazole or chlorphenesin.

27. A topical, foamable composition including an antifungal agent characterised in that upon application to the skin of a user a penetration of at least 10μg/cm^2 is achieved in the epidermis within one hour of application and sustained over a period of at least 23 hours.

28. A composition as claimed in claim 27 wherein the antifungal agent is ketoconazole and a penetration of at least 30μg/cm^2 is achieved in the epidermis within one hour of application and sustained over a period of at least 23 hours.

29. A composition as claimed in claim 27 wherein the antifungal agent is chlorphenesin and a penetration of at least 10μg/cm^2 is achieved in the epidermis within one hour of application and sustained over a period of at least 23 hours.

30. A method of treating fungal diseases including jock itch, tinea, dandruff and sebborheic dermatitis by applying to the affected area of a patient requiring such treatment the antifungal composition as claimed in any one of claims 1-29.

31. The use of an antifungal agent in the preparation of a topical foamable composition for the treatment of fungal diseases including jock itch, tinea, dandruff and sebborheic dermatitis, the topical foamable composition being characterised in that it is able to penetrate the epidermis of the skin and is retained in or on an area to be treated for a prolonged period of time, and in that it has a non-volatile component content of less than 25%.

FIG 1

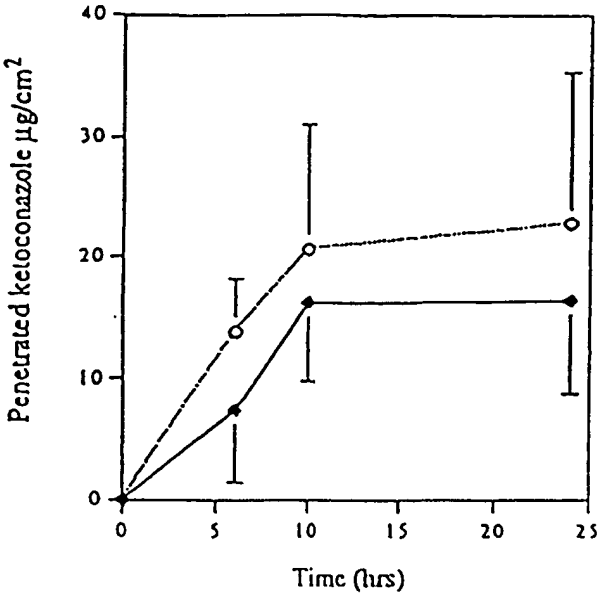

Penetrated ketoconazole µg/cm²
40
30
20
10
0
0
5
10
15
20
25
Time (hrs)

FIG 2

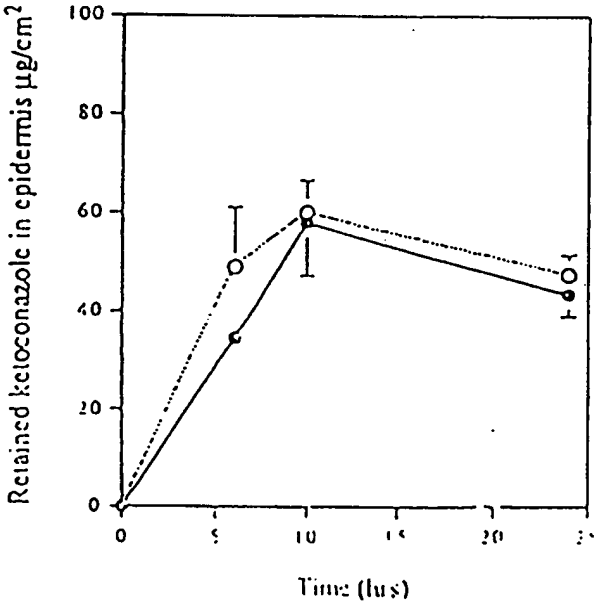

Retained ketoconazole in epidermis µg/cm²
100
80
60
40
20
0
0
10
Time (hrs)

Fig 3.

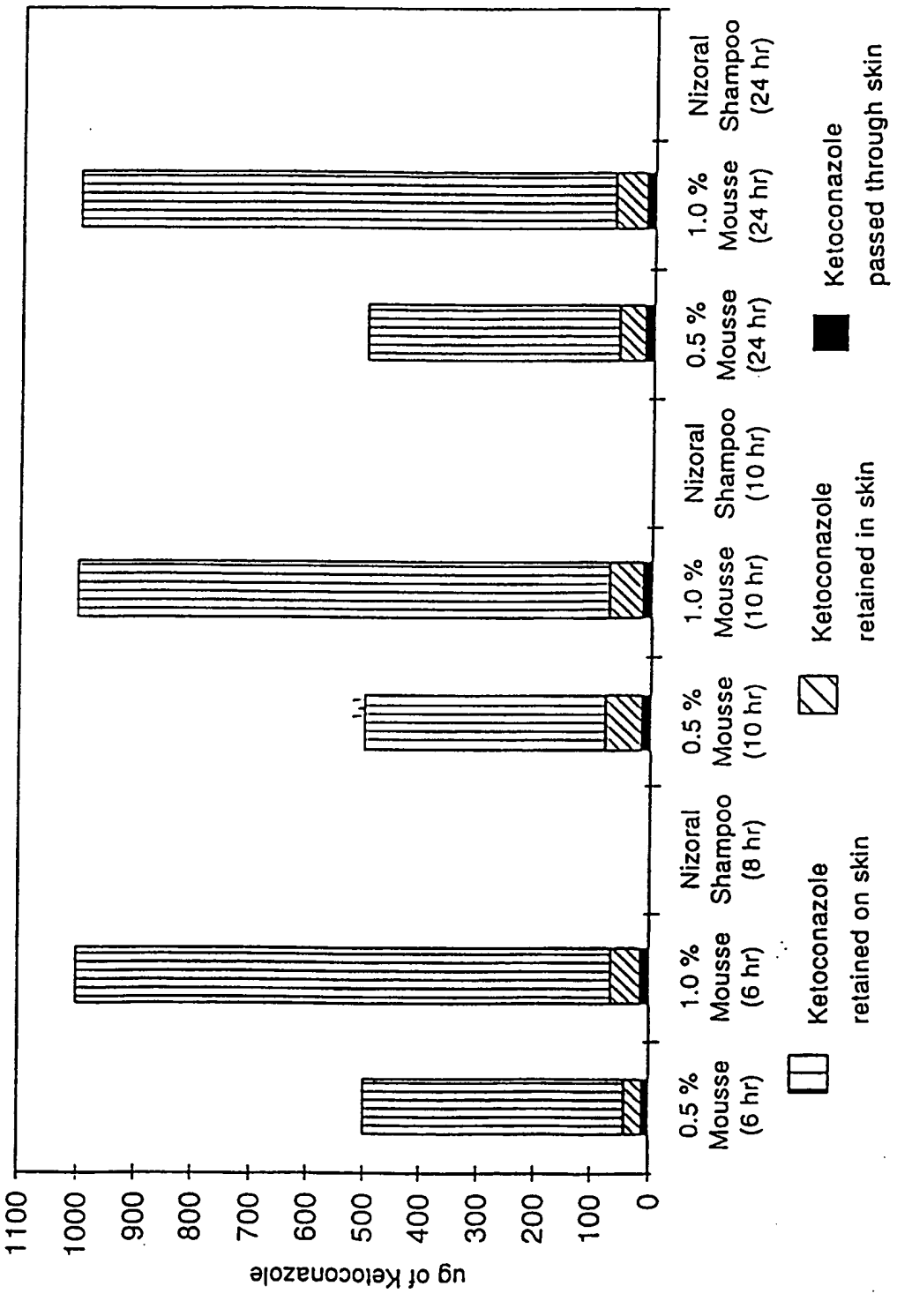

Ketoconazole Mousse vs Nizoral Shampoo
ug of Ketoconazole
1100
1000
900
800
700
600
500
400
300
200
100
0
0.5 % Mousse (6 hr)
1.0 % Mousse (6 hr)
Nizoral Shampoo (8 hr)
0.5 % Mousse (10 hr)
1.0 % Mousse (10 hr)
Nizoral Shampoo (10 hr)
0.5 % Mousse (24 hr)
1.0 % Mousse (24 hr)
Nizoral Shampoo (24 hr)
Ketoconazole retained on skin
Ketoconazole retained in skin
Ketoconazole passed through skin

FIG 4 3/4

HPLC Standard curve for ketoconazole

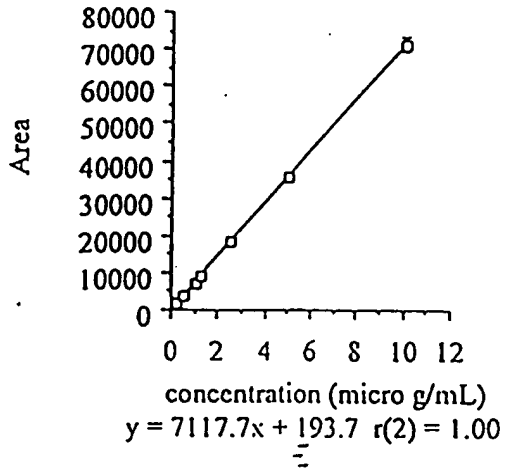


FIG 5

Ketoconazole assayed in skin at the time points studied

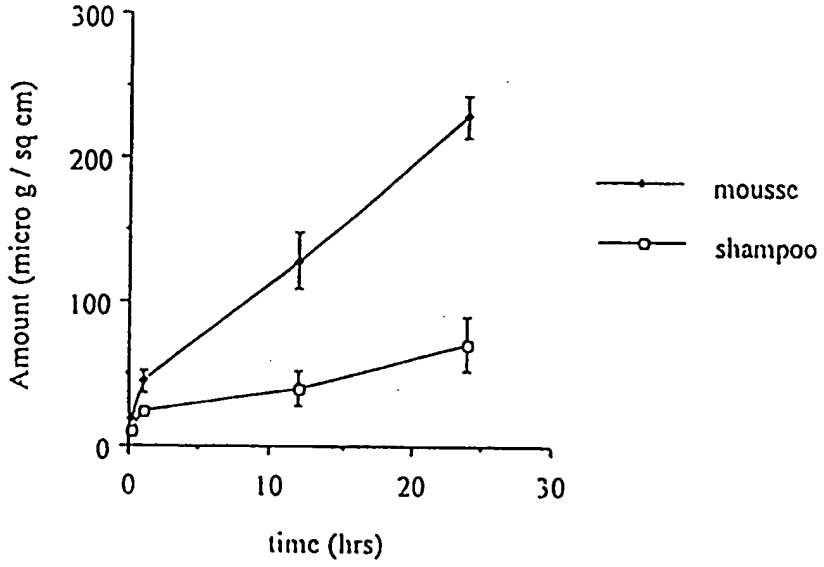
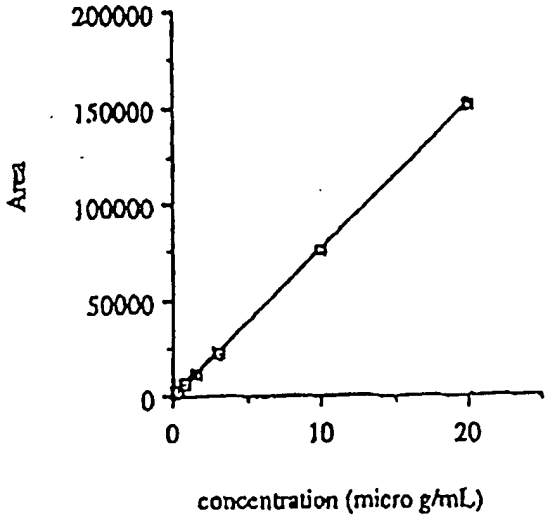
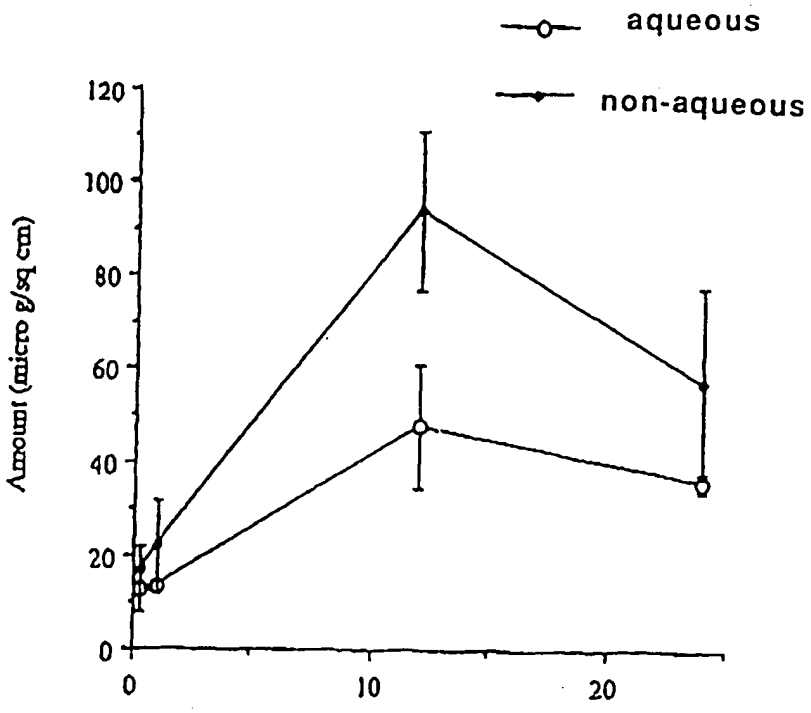


Figure 1 Ketoconazole retained in skin versus time after application of formulation. Data are the mean ± SEM (n=3) from Table 1.



$y = 7579.3x + 90.4$ $r^2 = 1.0$

FIG 7



INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00867

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 9/12, 7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: A61K 9/12, 7/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT: [FUNG:OR ANTIFUNG:OR JOCK:OR TINEA: OR DANDRUFF: OR SEBORRHEIC] AND [MOUSSE: OR FOAM: OR PROPELL: OR AEROSOL:] AND A61K 9/12 AND SKIN: AND SHAMPOO:
CAPLUS: [FUNG? OR ANTIFUNG? JOCK: OR TIMEA: OR DANDRUFF: OR SEBORRHEIC:] AND[MOUSSE: OR FOAM?] AND SHAMPOO: AND SKIN:

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, 97/17075 A(FABRE MEDICAMENT SA PIERRE) 15 May 1997 Whole specification	1-31
X	Patent Abstracts of Japan, JP, 08040899 A (OSAKA ZOSENSHO KK) 13 February 1996	1-4, 14-17, 30, 31

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 November 1998	14 DEC 1998
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer S. CHANDRA Telephone No.: (02) 6283 2264

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00867

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, 5456851 A (JOHNSON & JOHNSON CONSUMER PROD) 10 October 1995, Whole document	1-31
X	EP, 382619 A (L'OREAL SA) 16 August 1990, Whole document	1-4, 14-17, 30, 31
X	FR, 2616065 A (PABST JY) 9 December 1988, Whole document	1-4, 14-17, 30, 31
X	DE, 3630065 A (OSAKA AEROSOL IND) 5 March 1987	1-4, 14-17, 30, 31

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 98/00867

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	9717075	EP	862433	FR	2740685		
US	5456851	AU	21597/95	CA	2187030	EP	758879
		JP	9511740	WO	9527471		
FR	2704771	AU	66606/94	EP	648106	JP	7508766
		WO	9426238				
EP	382619	AU	49170/90	CA	2009607	DE	69000085
		JP	3020214	US	5171577		
DE	3630065	JP	62054784				

END OF ANNEX